

THAT WHICH IS CLAIMED:

1. A method for treating a human subject for a solid tumor comprising carcinoma cells expressing CD40 antigen, said method comprising administering to
5 said subject an effective amount of a human anti-CD40 monoclonal antibody that is capable of specifically binding to said CD40 antigen, said monoclonal antibody being free of significant agonist activity when bound to CD40 antigen, wherein said antibody is selected from the group consisting of:
- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
 - 10 b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
 - c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence
15 shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;
 - d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence
20 shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;
 - e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID
25 NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
 - f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
 - g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
 - 30 h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
 - i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

5 k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

2. The method of embodiment 1, wherein said monoclonal antibody binds to human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.
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3. The method of embodiment 1, wherein said fragment is selected from the group consisting of a Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and a single-chain Fv fragment.

15 4. The method of embodiment 1, wherein said solid tumor is selected from the group consisting of lung carcinoma, breast carcinoma, ovarian carcinoma, skin carcinoma, colon carcinoma, urinary bladder carcinoma, liver carcinoma, gastric carcinoma, prostate cancer, renal cell carcinoma, nasopharyngeal carcinoma, squamous cell carcinoma, thyroid papillary carcinoma, cervical carcinoma, and
20 sarcomas.

5. The method of embodiment 4, further comprising administering to said subject at least one other cancer therapy protocol selected from the group consisting of surgery, radiation therapy, chemotherapy, cytokine therapy, and other monoclonal
25 antibody intended for use in treatment of said solid tumor.

6. A method for treating a human subject for a solid tumor comprising carcinoma cells expressing CD40 antigen, said method comprising administering to said subject an effective amount of an antagonist anti-CD40 monoclonal antibody that
30 specifically binds Domain 2 of human CD40 antigen, wherein said antibody is free of significant agonist activity when bound to Domain 2 of human CD40 antigen.

7. The method of embodiment 6, wherein said antibody is a human antibody.
8. The method of embodiment 6, wherein said antibody has the binding specificity of an antibody selected from the group consisting of the antibody produced by hybridoma cell line 5.9 and the antibody produced by hybridoma cell line 12.12.
9. The method of embodiment 6, wherein said antibody is selected from the group consisting of the antibody produced by the hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5542 and the antibody produced by the hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5543.
10. The method of embodiment 6, wherein said antibody has the binding specificity of monoclonal antibody CHIR-12.12 or CHIR-5.9.
11. The method of embodiment 6, wherein said antibody binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12.
12. The method of embodiment 6, wherein said antibody is selected from the group consisting of:
- a) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;
 - b) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
 - c) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 12.12;

- d) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- e) a monoclonal antibody that competes with the monoclonal antibody CHIR-12.12 in a competitive binding assay;
- 5 f) a monoclonal antibody of any one of preceding items a)-e), wherein said antibody is recombinantly produced; and
- g) a monoclonal antibody that is an antigen-binding fragment of the CHIR-12.12 monoclonal antibody or an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-f), where the fragment retains the capability
- 10 of specifically binding to said human CD40 antigen.

13. The method of embodiment 6, wherein said solid tumor is selected from the group consisting of lung carcinoma, breast carcinoma, ovarian carcinoma, skin carcinoma, colon carcinoma, urinary bladder carcinoma, liver carcinoma, gastric

15 carcinoma, prostate cancer, renal cell carcinoma, nasopharyngeal carcinoma, squamous cell carcinoma, thyroid papillary carcinoma, cervical carcinoma, and sarcomas.

14. The method of embodiment 13, further comprising administering to

20 said subject at least one other cancer therapy protocol selected from the group consisting of surgery, radiation therapy, chemotherapy, cytokine therapy, and other monoclonal antibody intended for use in treatment of said solid tumor.

15. A method for inhibiting the growth of a solid tumor comprising

25 carcinoma cells expressing CD40 antigen, said method comprising contacting said cells with an effective amount of a human anti-CD40 monoclonal antibody that is capable of specifically binding to said CD40 antigen, said monoclonal antibody being free of significant agonist activity when bound to CD40 antigen, wherein said antibody is selected from the group consisting of:

30 a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;

b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

- 5 c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;
- 10 d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;
- e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
- 15 f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- 20 h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;
- j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and
- 25 k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

16. The method of embodiment 15, wherein said monoclonal antibody
30 binds to human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.

17. The method of embodiment 15, wherein said fragment is selected from the group consisting of a Fab fragment, an F(ab')₂ fragment, an Fv fragment, and a single-chain Fv fragment.
- 5 18. The method of embodiment 15, wherein said solid tumor is selected from the group consisting of lung carcinoma, breast carcinoma, ovarian carcinoma, skin carcinoma, colon carcinoma, urinary bladder carcinoma, liver carcinoma, gastric carcinoma, prostate cancer, renal cell carcinoma, nasopharyngeal carcinoma, squamous cell carcinoma, thyroid papillary carcinoma, cervical carcinoma, and
10 sarcomas.
19. The method of embodiment 18, further comprising administering to said subject at least one other cancer therapy protocol selected from the group consisting of surgery, radiation therapy, chemotherapy, cytokine therapy, and other
15 monoclonal antibody intended for use in treatment of said solid tumor.
20. A method for inhibiting the growth of a solid tumor comprising carcinoma cells expressing CD40 antigen, said method comprising contacting said cells with an effective amount of an antagonist anti-CD40 monoclonal antibody that
20 specifically binds Domain 2 of human CD40 antigen, wherein said antibody is free of significant agonist activity when bound to Domain 2 of human CD40 antigen.
21. The method of embodiment 20, wherein said antibody is a human antibody.
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22. The method of embodiment 20, wherein said antibody has the binding specificity of an antibody selected from the group consisting of the antibody produced by hybridoma cell line 5.9 and the antibody produced by hybridoma cell line 12.12.
- 30 23. The method of embodiment 20, wherein said antibody is selected from the group consisting of the antibody produced by the hybridoma cell line deposited

with the ATCC as Patent Deposit No. PTA-5542 and the antibody produced by the hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5543.

24. The method of embodiment 20, wherein said antibody has the binding
5 specificity of monoclonal antibody CHIR-12.12 or CHIR-5.9.

25. The method of embodiment 20, wherein said antibody binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12.

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26. The method of embodiment 20, wherein said antibody is selected from the group consisting of:

- a) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence
15 shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;
- b) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group
20 consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
- c) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 12.12;
- d) a monoclonal antibody that binds to an epitope comprising residues 82-
25 87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- e) a monoclonal antibody that competes with the monoclonal antibody CHIR-12.12 in a competitive binding assay;
- f) a monoclonal antibody of any one of preceding items a)-e), wherein said antibody is recombinantly produced; and
- 30 g) a monoclonal antibody that is an antigen-binding fragment of the CHIR-12.12 monoclonal antibody or an antigen-binding fragment of a monoclonal

antibody of any one of preceding items a)-f), where the fragment retains the capability of specifically binding to said human CD40 antigen.

27. The method of embodiment 20, wherein said solid tumor is selected
5 from the group consisting of lung carcinoma, breast carcinoma, ovarian carcinoma, skin carcinoma, colon carcinoma, urinary bladder carcinoma, liver carcinoma, gastric carcinoma, prostate cancer, renal cell carcinoma, nasopharyngeal carcinoma, squamous cell carcinoma, thyroid papillary carcinoma, cervical carcinoma, and sarcomas.

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28. The method of embodiment 27, further comprising administering to said subject at least one other cancer therapy protocol selected from the group consisting of surgery, radiation therapy, chemotherapy, cytokine therapy, and other monoclonal antibody intended for use in treatment of said solid tumor.

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